ABSTRACT

Background: Cosmeceutical products represent an increasingly important therapeutic option for anti-aging and rejuvenation, either used alone or in combination with dermatologic surgical procedures. Among this group of products, topical growth factors have demonstrated efficacy in randomized, controlled clinical trials. However, comparisons between different products remain uncommon. **Objective:** The objective of this randomized, double-blind, split-face clinical trial was to compare two different topical growth factor formulations derived from either human fibroblasts or human adipose tissue derived mesenchymal stem cells. **Methods:** This was an institutional review board-approved, randomized, double-blind, split-face clinical trial involving 20 healthy subjects with moderate-to-severe facial wrinkling secondary to photodamage. One half of the face was randomized to receive topical human fibroblast growth factors and the other topical human mesenchymal stem cell growth factors. Treatment was continued for three months, and evaluations were performed in a double-blind fashion. **Results:** Both growth

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ORIGINAL RESEARCH

A Prospective, Randomized, Double-blind, Split-face Clinical Trial Comparing the Efficacy of Two Topical Human Growth Factors for the Rejuvenation of the Aging Face

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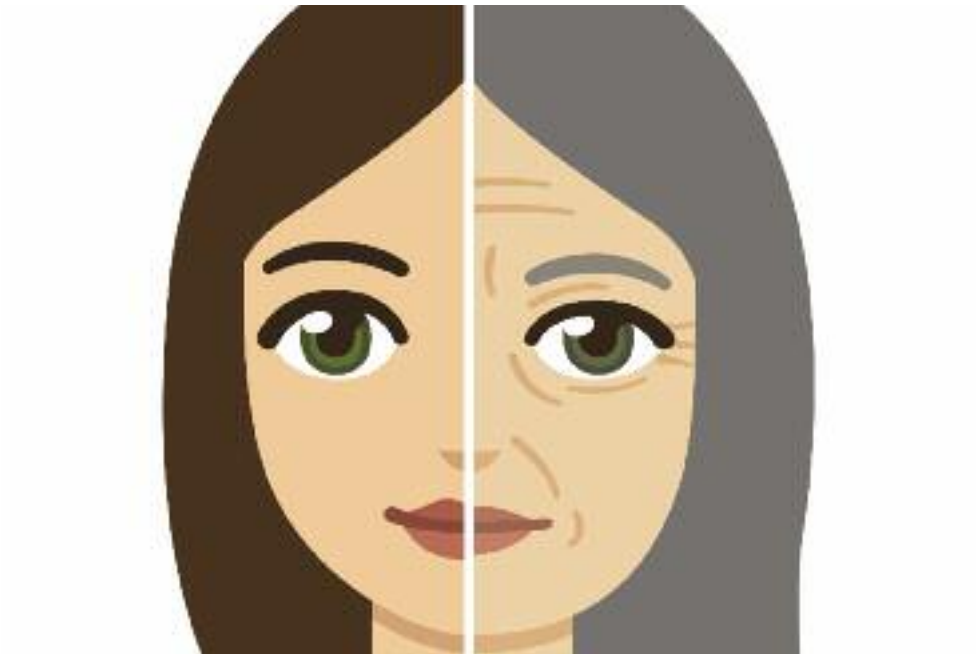

FACIAL RHYTIDES ARE A significant concern among patients presenting to cosmetic dermatology clinics. They typically result from accumulated photodamage and may be exacerbated by muscular hyperactivity and age-related volume loss. At the molecular level, ultraviolet radiation causes increased oxidative stress, tissue damage, and the accumulation of free radicals, which result in the suppression of endogenous growth factors and the progressive degradation of the collagen and elastin

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factor formulations achieved significant improvement in facial wrinkling. Blinded investigator and subject evaluations did not detect any significant differences between the two formulations in terms of efficacy, safety, or tolerability. **Conclusion:** Both human fibroblast growth factors and human mesenchymal stem cell growth factors are effective at facial rejuvenation. Topical growth factors represent a useful therapeutic modality.

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networks within the dermis.[1]

In order to address this issue, topical formulations containing growth factors that aim to augment the natural regenerative ability of the dermis have been explored.[2] One such formulation, based on growth factors derived from human fibroblasts of neonatal foreskin origin (TNS Essential Serum, SkinMedica, Allergan), has demonstrated clinical efficacy in skin rejuvenation. When applied to the face of 14 patients twice daily for 60 days, 78.6 percent demonstrated significant clinical improvements in photodamage.[3] A subsequent double-blind, randomized, vehicle-controlled study involving 60 patients showed improvements in fine lines, skin tone and texture, and hyperpigmentation after three months of application.[4]

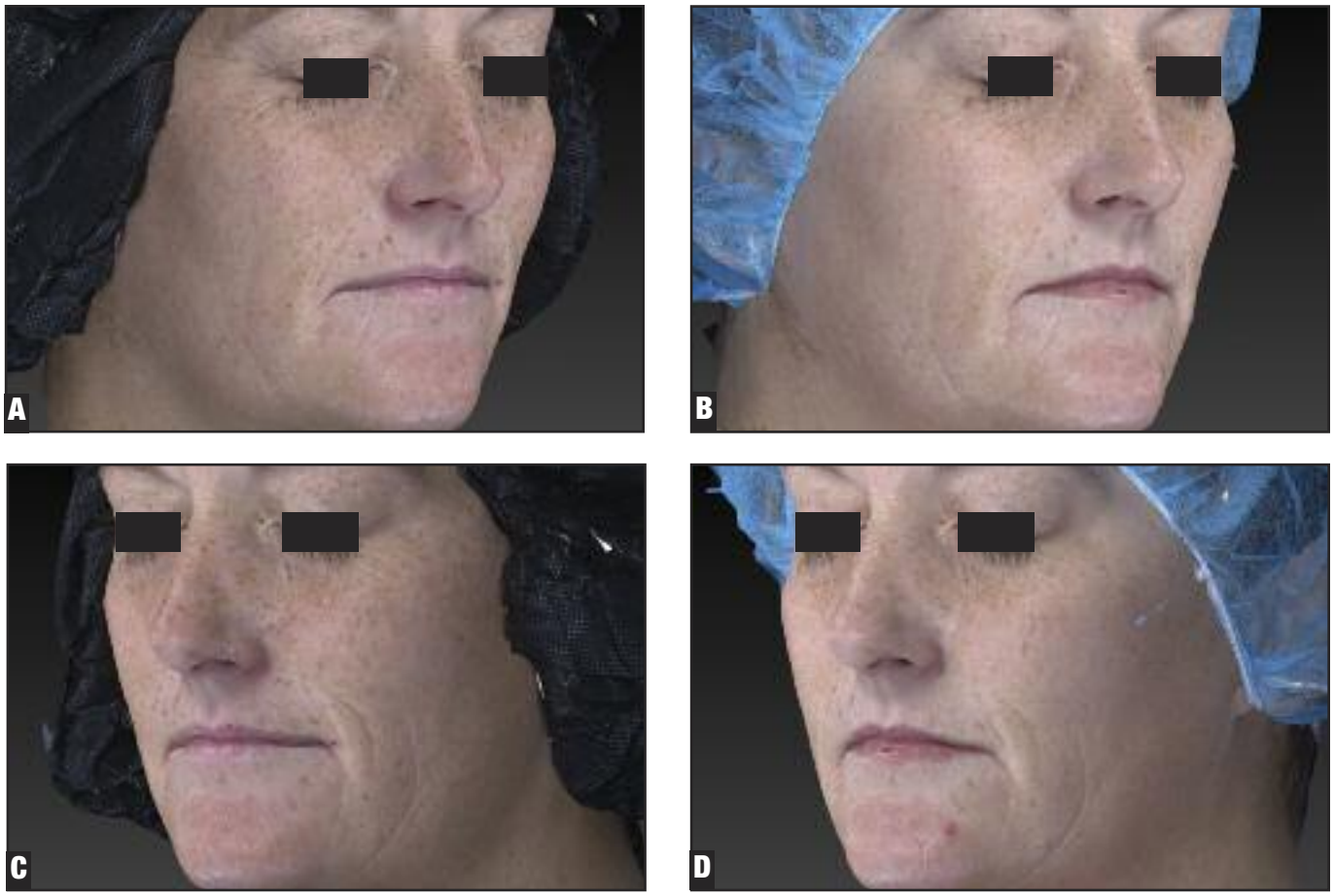
Another source of human growth factors is mesenchymal stem cells (MSC) derived from adipose tissue. Medium containing growth factors secreted by this population of stem cells has demonstrated efficacy in promoting hair regrowth[5]; alteration of matrix metalloproteinase (MMP) expression in dermal fibroblasts that have been exposed to ultraviolet radiation (UVR)[6]; and modulating endothelial cell, fibroblast, and keratinocyte migration.[7] These phenomena may have potential benefit in addressing cutaneous photodamage and subsequent wrinkling and elastosis. However, controlled clinical trials evaluating the safety and efficacy of MSC conditioned medium in improving rhytides are lacking.

In this prospective, randomized, double-blind, split-face clinical trial, the authors compare the efficacy of growth factors derived from human fibroblasts versus human MSC for facial rejuvenation.

MATERIALS AND METHODS

Study design. This was a prospective, randomized, double-blind, split-face, institutional review board (IRB)-approved clinical trial that was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization. After obtaining informed consent, 20 female subjects over the age of 18 with moderate-to-severe facial wrinkling were enrolled. Subjects were excluded if they were pregnant or breastfeeding; had treatment with any neuromodulator, energy device, chemical peel, or soft tissue filler within the previous six months; had applied any topical products containing vitamins A, C, or E derivatives, alpha-hydroxy acids, or salicylic acids within the previous two weeks or at any time during the trial; or had any pre-existing dermatological condition in the facial region.

Study intervention. Ten subjects were randomized to receive MSC-conditioned growth factor formulation (NuGene Universal Serum, NuGene) to the right side of the face and human fibroblast-conditioned growth factor formulation (TNS Essential Serum, SkinMedica, Allergan) to the left side of the face, and 10 were randomized in opposite fashion. Both subject and investigator were blinded to the treatment halves. The test products were applied twice daily for a period of three months, with follow-up visits conducted at 1, 2, and 3 months. Other than a provided gentle cleanser and physical sunblock, subjects did not apply any additional topical products for the duration of the study. Baseline and follow-up photography was obtained utilizing the Canfield Vectra 3-dimensional imaging system (Canfield Scientific).



Figures 1A–1D. Clinical improvement in wrinkling seen after three months of topical growth factor application. Both test products demonstrated significant reduction in blinded wrinkle evaluations as compared with baseline. A and B are before and after human fibroblast growth factor application. C and D are before and after human MSC growth factor application. Global facial wrinkle improvements are noted on both sides with particularly striking improvements seen periorbitally.

Evaluation of efficacy. Both subject and evaluating investigator were blinded to the treatment halves. Facial wrinkling was assessed by the blinded evaluator at baseline and at each follow-up visit via a standardized 5-point scale (1=absent wrinkling, 2=shallow but visible wrinkling, 3=moderately deep wrinkling, 4=deep wrinkling with well-defined edges, 5=very deep wrinkling with redundant folds). The blinded evaluator also assessed percentage improvement in rhytids, skin texture, and skin firmness at each follow-up visit based on a 4-point scale (1-0-25% improvement, 2-26-50% improvement, 3-51-75% improvement, 4-76-100% improvement). Subjects rated their percentage improvement utilizing the same scale and this was done independently of the investigator evaluation.

Statistical analysis. Statistical evaluation was performed with Microsoft Excel 2013. The two-tailed Student's *t*-test was utilized to determine the difference in means between groups.

RESULTS

Assessment of wrinkling. There was a significant improvement in wrinkling with both test products beginning at Month 2 of evaluation and persisting until Month 3 and the end of the study as compared to baseline (Figure 1). No statistical difference was detected between the two groups (Figure 2).

Assessment of improvement. Rhytids, skin texture, and firmness improved from 29 to 41 percent according to the blinded investigator

Table 1. Improvement in rhytids, skin texture, and skin firmness after application of topical growth factors as assessed by the blinded evaluator; no significant differences detected between the two test products

	WRINKLES (MEAN PERCENTAGE IMPROVEMENT AFTER 3 MONTHS APPLICATION)	SKIN TEXTURE (MEAN PERCENTAGE IMPROVEMENT AFTER 3 MONTHS APPLICATION)	SKIN FIRMNESS (MEAN PERCENTAGE IMPROVEMENT AFTER 3 MONTHS APPLICATION)
TEST PRODUCT			
Human fibroblast growth factor	41%	40%	31%
Human mesenchymal stem cell growth	34%	40%	29%
***P* value**	0.23	1	0.68

Table 2. Improvement in rhytids, skin texture, and skin firmness after application of topical growth factors as assessed by the blinded subject; no significant differences detected between the two test products

	WRINKLES (MEAN PERCENTAGE IMPROVEMENT AFTER 3 MONTHS APPLICATION)	SKIN TEXTURE (MEAN PERCENTAGE IMPROVEMENT AFTER 3 MONTHS APPLICATION)	SKIN FIRMNESS (MEAN PERCENTAGE IMPROVEMENT AFTER 3 MONTHS APPLICATION)
TEST PRODUCT			
Human fibroblast growth factor	46%	54%	47%
Human mesenchymal stem cell growth	38%	49%	41%
***P* value**	0.27	0.46	0.39

at three months. Subject reported slightly higher degrees of improvements, ranging between 38 and 54 percent. Once again, no statistical difference between the two test products was detected (Tables 1 and 2).

DISCUSSION

In this study, we demonstrate the equivalent efficacy between a clinically proven growth factor formulation and a novel preparation based on human MSC-conditioned medium. Blinded evaluations from both investigator and subject revealed no appreciable difference between the two products in terms of wrinkle improvement, skin firming, and reduction of rough skin texture. Furthermore, both products produced a clinically significant

improvement in rhytids, adding further evidence for topical growth factors as a safe and effective anti-aging therapeutic modality. The limitations of this study include the relatively small sample size and the inability to completely rule out the possibility of the tested topical growth factor formulations having a locally diffuse effect even if initial application was restricted to one half of the face.

Over the past two decades, accumulating evidence has suggested that topical growth factor formulations are both safe and effective for skin rejuvenation.[8–10] However, the precise mechanism of action of these formulations has yet to be fully elucidated. Studies have demonstrated that molecules larger than 500Da in molecular weight cannot penetrate intact stratum corneum.[9] Growth factors are typically in the 15,000Da range and therefore should have minimal penetrative ability. The hypothesis is that topical growth factors gain access to the dermis via penetration of hair follicles. Once in the dermis, they act as cellular messengers, which trigger signaling cascades resulting in keratinocyte activation, proliferation, and production of endogenous growth factors that serve to reinforce and amplify the signaling loop. Despite continuing gaps in the understanding of how topical growth factors achieve their effects, their clinical efficacy has been demonstrated in multiple clinical trials.[3,4,11–13] Further evaluation of novel agents and mechanisms of action will help to refine our approach to skin rejuvenation.

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